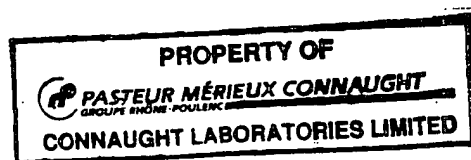# Vaccines

Third Edition

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5 General Immunization Practices

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Recommendations for immunization practices are based on scientific knowledge of vaccine characteristics, the principles of immunization, and the epidemiology of specific diseases. In addition, the experience and judgment of public health officials and specialists in clinical and preventive medicine play a key role in developing recommendations that maximize the benefits and minimize the risks and costs associated with immunization. General guidelines for immunization practices are based on evidence and expert opinion of the benefits, costs, and risks of vaccination as they apply to the current epidemiology of disease and use of vaccines in the United States. However, many of the principles are universal and are applicable to other countries with different public health infrastructures.

VACCINE STORAGE AND HANDLING

Vaccines must be properly shipped, stored, and handled to avoid loss of their biological activity. Recommended storage and handling requirements for each vaccine are given in the manufacturer's product label.[1] Correct shipping, storage, and handling practices are also published in the recommendations of the major vaccine policymaking committees, such as the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention and the American Academy of Pediatrics (AAP) (see Chapter 42).[2-4] Failure to adhere to these requirements can lead to a loss of vaccine potency, resulting in an inadequate immune response in the vaccinee. Visible evidence of altered vaccine integrity may or may not be present. The manufacturer should be contacted when questions arise about the correct handling of a vaccine. New vaccines or new formulations of an existing vaccine may have different shipping, storage, and handling requirements. Table 5–1 gives recommended storage practices for the most commonly used vaccines in the United States.

Exposure to either higher or lower temperatures than

recommended can inactivate a vaccine (see Table 5–1). For example, live virus vaccines such as oral poliovirus vaccine (OPV) and varicella are sensitive to temperatures above freezing and should be kept frozen until just before administration. Measles-mumps-rubella (MMR) vaccine and yellow fever vaccine should be kept frozen, although storage at below 8°C (46°F) and below 5°C (41°F), respectively, is acceptable.[3, 5] However, vaccines composed of purified antigens or inactivated microorganisms, such as hepatitis A, hepatitis B, *Haemophilus. influenzae* type b (Hib), and influenza, can lose their potency if frozen and therefore should be kept at 2 to 8°C (36 to 46°F) and never frozen.[3, 4] Diluents should not be frozen.[3, 4]

Maintenance of a "cold chain" from vaccine production to use helps ensure vaccine potency at the time of administration.[3, 4] Temperature monitoring and control is important for all storage and handling, particularly during transport and field use. Temperatures should be monitored regularly, using a thermometer that records current, maximum, and minimum temperatures. Whereas maintenance of cold and freezing temperatures is a problem in tropical climates, recent data suggest that inappropriate freezing of inactivated vaccines is a problem in maintaining vaccine stability in cold and temperate climates.[6] Kendal and associates[4, 6] have suggested methods for packing and shipping vaccines based on tests conducted under representative conditions within the United States. Shipping containers should be sturdy and the correct size for the amount of vaccine to be shipped. Appropriate insulation (e.g., panels and boxes of polystyrene, isocyanurate, or polyurethane) and cold source (e.g., dry ice, gel packs, or bottles with frozen liquid) should be used to maintain the recommended temperature. Loose fillers do not provide reliable temperature insulation.

Vaccines should not be reconstituted until immediately before use. If it is not administered within the time interval recommended by the manufacturer, reconstituted vaccine should be discarded.[3] With the exception of OPV, live virus vaccines should not be refrozen after

Table 5-1. RECOMMENDED STORAGE CONDITIONS FOR COMMONLY USED VACCINES*

VACCINE	RECOMMENDED TEMPERATURE	DURATION OF STABILITY†	NORMAL APPEARANCE
Diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed (DTaP)	2–8°C. Do not freeze. As little as 24 hr at <2°C or >25°C may cause antigens to fall from suspension and be difficult to resuspend.	Not more than 18 mo from the time of issue from manufacturer's cold storage	Markedly turbid and whitish suspension. If product contains clumps of material that cannot be resuspended with vigorous shaking, it should *not* be used.
Diphtheria and tetanus toxoids and whole-cell pertussis vaccine, adsorbed (DTP)	2–8°C. Do not freeze. As little as 24 hr at <2°C or >25°C may cause antigens to fall from suspension and be difficult to resuspend.	Not more than 18 mo from the time of issue from manufacturer's cold storage	Markedly turbid and whitish suspension. If product contains clumps of material that cannot be resuspended with vigorous shaking, it should *not* be used.
Diphtheria and tetanus toxoids, whole-cell pertussis vaccine adsorbed, and *Haemophilus* b conjugate vaccine (DTP-HbOC)	2–8°C. Do not freeze. As little as 24 hr at <2°C or >25°C may cause antigens to fall from suspension and be difficult to resuspend.	Not more than 18 mo from the time of issue from manufacturer's cold storage	Markedly turbid, white suspension. If product contains clumps of material that cannot be resuspended with vigorous shaking, it should *not* be used.
Diphtheria toxoid, adsorbed	2–8°C. Do not freeze.	Not more than 2 yr from the time of issue from manufacturer's cold storage	Turbid and white, slightly gray, or slightly pink suspension
Haemophilus b conjugate vaccine: HbOC (diphtheria CRM197 protein conjugate)	2–8°C. Do not freeze.	Not more than 2 yr from date of issue from manufacturer's cold storage	Clear, colorless liquid
Haemophilus b conjugate vaccine: PRP-D (diphtheria toxoid conjugate)	2–8°C. Do not freeze.	Not more than 2 yr from date of issue from manufacturer's cold storage	Clear, colorless liquid
Haemophilus b conjugate vaccine: PRP-OMP (meningococcal protein conjugate)	Lyophilized formulation: 2–8°C. Do not freeze formulation or diluent. Reconstituted formulation: 2–8°C. Do not freeze.	Not more than 2 yr from date of issue from manufacturer's cold storage Discard reconstituted vials if not used within 24 hr	Reconstituted: after agitation, slightly opaque, white suspension
Haemophilus b conjugate vaccine: PRP-T (tetanus toxoid conjugate)	Lyophilized formulation: 2–8°C. Do not freeze formulation or diluent. May be reconstituted with DTP produced by Connaught Laboratories. Reconstituted formulation: 2–8°C. Do not freeze.	Not more than 2 yr from date of issue from manufacturer's cold storage Vaccine should be used immediately when reconstituted	Reconstituted: clear and colorless
Hepatitis A vaccine, inactivated	2–8°C. Do not freeze. Do not use if product has been frozen.	2 yr, if kept refrigerated	Opaque, white suspension
Hepatitis B virus vaccine, inactivated (recombinant)	2–8°C. Storage outside this temperature range may reduce potency. Freezing substantially reduces potency.	2 yr from date of issue from manufacturer's cold storage	After thorough agitation, a slightly opaque, white suspension
Influenza virus vaccine (subvirion)	2–8°C. Freezing destroys potency.	Vaccine is recommended only during the year for which it is manufactured; antigenic composition differs annually	Clear, colorless liquid

Vaccine	Storage	Expiration/discard	Appearance
Measles-mumps-rubella virus (MMR) vaccine, live	Lyophilized formulation: 2–8°C, but may be frozen. Protect from light, which may inactivate virus. Diluent: store at room temperature or refrigerated, do not freeze. Reconstituted formulation: 2–8°C. Protect from light, which may inactivate virus.	Discard reconstituted vials if not used within 8 hr	Reconstituted: clean, yellow solution
Measles virus vaccine, live	See MMR	See MMR	See MMR
Mumps virus vaccine, live	See MMR	See MMR	See MMR
Rubella virus vaccine, live	See MMR	See MMR	See MMR
Pneumococcal vaccine, polyvalent	2–8°C. Freezing destroys potency.	See expiration date on vial	Clear, colorless, or slightly opalescent liquid
Poliovirus vaccine, inactivated (IPV)	2–8°C. Do not freeze.	Not more than 1 yr from date of issue from manufacturer's cold storage	Clear, colorless suspension. Vaccine that contains particulate matter, develops turbidity, or changes in color should *not* be used.
Poliovirus vaccine, live, oral (OPV)	Must be stored at <0°C. Because of sorbitol in the vaccine, it will remain fluid at temperatures above −14°C. Refreezing the thawed product is acceptable (maximum of 10 thaw-freeze cycles), if the temperature never exceeds 8°C, and the cumulative thawing time is <24 hr.	Not more than 1 yr from date of issue from manufacturer's cold storage	Clear solution, usually red or pink, from the phenol red (pH indicator) it contains; may have a yellow color if shipment was packed with dry ice. Color changes that occur during storage or thawing are unimportant, provided the solution remains clear.
Tetanus and diphtheria toxoids, adsorbed (DT and Td)	2–8°C. Do not freeze.	Not more than 2 yr from the time of issue from manufacturer's cold storage	Markedly turbid and white suspension. If product contains clumps of material that cannot be resuspended with vigorous shaking, it should *not* be used.
Varicella virus vaccine†	Lyophilized formulation: keep frozen, at temperature of −15°C or colder. Protect from light. Diluent: store at room temperature or refrigerated. Reconstituted formulation: use immediately; do not store. For temporary storage, unreconstituted vaccine may be stored at 2–8°C for a maximum of 72 hr.	Lyophilized formulation: 18 mo. Discard reconstituted vials if not used within 30 min. Discard if not used within 72 hr (do not refreeze)	Lyophilized formulation: whitish powder. Reconstituted formulation: clear, colorless to pale yellow liquid

*For recently licensed combination vaccines, see package inserts; instructions may be different from those for products listed in the table. Also, any changes in the formulation of currently available immunizing agents may alter their appearance, stability, and storage requirements.
†Questions regarding the stability of biologicals subjected to potentially harmful environmental conditions should be addressed to the manufacturer of the product in question.
‡For questions concerning stability, contact the manufacturer by calling 1-800-9-VARIVAX.
From American Academy of Pediatrics. Active immunization. In Peter G (ed), 1997 Red Book: Report of the Committee on Infectious Diseases (24th ed). Elk Grove Village, IL, American Academy of Pediatrics, 1997, pp 4–36.

thawing (see Table 5–1). Certain vaccines (e.g., MMR and varicella) must also be protected from light to prevent inactivation of the vaccine virus.

ADMINISTRATION OF VACCINES

Complete and accurate records documenting the administration of all vaccines should be maintained by both healthcare providers who administer vaccines and vaccine recipients (or their parents). For each immunization, the following information should be recorded: (1) date of vaccination; (2) product administered, manufacturer, lot number, and expiration date; (3) site and route of administration; and (4) name, address, and title of healthcare provider administering the vaccine.

Infection Control and Sterile Injection Technique

Infection resulting from administration of vaccines is unlikely if appropriate precautions are used. Hand washing before and after injecting vaccines is indicated to reduce the risk of bacterial contamination and transmission of infection between recipients and healthcare personnel. In general, the use of protective gloves is not necessary when administering vaccines unless the healthcare worker will have contact with potentially infectious body fluids or has open lesions on the hands.[2, 7]

Failure to follow relevant infection control guidelines can result in the transmission of bloodborne pathogens or bacterial infection and abscess formation. Contamination of an injection site can occur from bacteria on the skin at the site of injection. To prevent such contamination, the skin at the injection site should be prepared with isopropyl alcohol (70%) or another disinfecting agent and allowed to dry before injection.[8] Transmission of pathogens can also occur if needles, syringes, vaccines, or other equipment used to administer vaccines becomes contaminated.

To prevent such contamination, syringes and needles must be sterile. A separate needle and syringe should be used for each injection. Disposable needles and syringes should be discarded after a single use in a labeled, puncture-proof container to prevent inadvertent needle stick injury or reuse. Because recapping and removing a used needle from a syringe can result in injury to the user, needles should not be recapped after use.[2] The needle and syringe should be discarded as a single unit without removing the needle from the syringe. Single-use disposable needles and syringes should not be sterilized and reused.

If only reusable (i.e., nondisposable) needles and syringes are available, they must be thoroughly cleaned and sterilized after each injection to prevent transmission of bloodborne or other pathogens between patients. Reusable syringes are usually glass rather than plastic. Because of its inert characteristics, glass can be cleaned and sterilized more easily than plastic. Because hypodermic needles enter deep tissues, great care must be taken to ensure that all contaminant is removed from the needle and syringe.[8, 9] Liquid germicides alone are insufficient for needle sterilization because of the restricted access of the chemical agent to the narrow lumen of the needle.[9] Strict adherence to the recommended time and temperature for the sterilization procedure used must be observed.[8]

Route of Administration

One or more routes of administration (i.e., intramuscular, subcutaneous, intradermal, intranasal, or oral) are recommended for each vaccine and are listed both in the manufacturer's product label and in published recommendations of immunization advisory committees (Table 5–2).[2, 7] These routes are usually determined during prelicensure vaccine studies and are based on vaccine composition and immunogenicity. Vaccines should be administered in sites where they elicit the desired immune response and where the likelihood of local tissue, neural, or vascular injury is minimal.[2] To avoid unnecessary local and systemic adverse events and to ensure the appropriate immune response, persons administering vaccines should not deviate from the recommended route of administration in the product label unless specific data can be cited to justify an alternative route. A route of administration or anatomical site of injection different from that recommended can result in an inadequate immune response. For example, the immunogenicity of hepatitis B vaccine and rabies vaccine is substantially lower when the gluteal instead of the deltoid vaccination site is used.[10, 11] The reduced immunogenicity is presumably due to inadvertent injection into subcutaneous or deep fatty tissue rather than muscle.[12, 13]

Deep intramuscular injection is generally recommended for adjuvant-containing vaccines because subcutaneous or intradermal administration can cause marked local irritation, induration, skin discoloration, inflammation, and granuloma formation.[2, 7] However, subcutaneous injection can lessen the risk of local neurovascular injury and is recommended for vaccines, such as live virus vaccines, that are nonreactogenic and highly immunogenic when administered by this route. Intradermal administration is preferred for live bacille Calmette-Guérin (BCG) vaccine and is sometimes used for certain rabies and typhoid vaccines.[14–16]

Care should be taken to ensure that vaccines are not injected into a blood vessel. Accordingly, the needle should be inserted into the recommended site and the plunger should be pulled back before the vaccine is injected. If blood appears in the needle hub, the needle should be withdrawn and the injection made at another site. This procedure should be repeated until no blood appears in the needle hub, at which point the vaccine can be administered.

Subcutaneous Injections

Vaccines are usually administered into the thigh of infants and the deltoid region of older children and adults. A 5/8- to 3/4-inch, 23- to 25-gauge needle is recommended in most situations.[2, 7] The needle is inserted into the tissues below the dermal layer of the skin. To avoid administering the vaccine into a muscle, the skin

Table 5–2. LICENSED VACCINES AND TOXOIDS AVAILABLE IN THE UNITED STATES, BY TYPE AND RECOMMENDED ROUTES OF ADMINISTRATION

VACCINE	TYPE	ROUTE
Adenovirus*	Live virus	Oral
Anthrax†	Inactivated bacteria	Subcutaneous
BCG (bacille Calmette-Guérin)	Live bacteria	Percutaneous (intradermal)
Cholera	Inactivated bacteria	Subcutaneous; intramuscular; intradermal‡
Diphtheria-tetanus-pertussis (DTP)	Toxoids; inactivated whole bacteria	Intramuscular
Diphtheria–tetanus–acellular pertussis (DTaP)	Toxoids; inactivated bacterial components	Intramuscular
Hepatitis A	Inactivated virus	Intramuscular
Hepatitis B	Inactivated viral antigen	Intramuscular
Haemophilus influenzae type b conjugate (Hib)	Bacterial polysaccharide conjugated to protein	Intramuscular
Hib-DTP	Bacterial polysaccharide conjugated to protein; toxoids; inactivated whole bacteria	Intramuscular
Hib-DTaP	Bacterial polysaccharide conjugated to protein; toxoids; inactivated bacterial components	Intramuscular
Hib–hepatitis B	Bacterial polysaccharide conjugated to protein; inactivated viral antigen	Intramuscular
Influenza	Inactivated whole virus or viral components	Intramuscular
Japanese encephalitis	Inactivated virus	Subcutaneous
Measles	Live virus	Subcutaneous
Measles-mumps-rubella (MMR)	Live virus	Subcutaneous
Meningococcal	Bacterial polysaccharide (serotypes A/C/Y/W-135)	Subcutaneous
Mumps	Live virus	Subcutaneous
Pertussis†	Inactivated whole bacteria	Intramuscular
Plague	Inactivated bacteria	Intramuscular
Pneumococcal	Bacterial polysaccharide (23 serotypes)	Intramuscular; subcutaneous
Poliovirus, inactivated (IPV)	Inactivated virus	Subcutaneous
Poliovirus, oral (OPV)	Live virus	Oral
Rabies	Inactivated virus	Intramuscular; intradermal§
Rubella	Live virus	Subcutaneous
Tetanus	Toxoid (inactivated toxin)	Intramuscular
Tetanus-diphtheria (Td or DT)‖	Toxoids (inactivated toxins)	Intramuscular
Typhoid		
Live oral/Ty21a	Live bacteria	Oral
Vi polysaccharide	Capsular polysaccharide	Intramuscular
Heat-phenol–inactivated	Inactivated whole bacteria	Subcutaneous¶
Varicella	Live virus	Subcutaneous
Yellow fever	Live virus	Subcutaneous

*Available only to the U.S. Armed Forces.
†Distributed by Michigan Biological Products Institute, Michigan Department of Public Health.
‡The intradermal dose is lower than the subcutaneous dose.
§The intradermal dose of rabies vaccine, human diploid cell (HDCV), is lower than the intramuscular dose and is used only for preexposure vaccination. Rabies vaccine, adsorbed, should not be used intradermally.
‖Td, tetanus and diphtheria toxoids for use in persons 7 years of age and older; DT, tetanus and diphtheria toxoids for use in children younger than 7 years.
¶Booster doses may be administered intradermally.

and subcutaneous tissue can be held gently between the thumb and fingers to raise it above the muscle layer. The needle is inserted into the resulting skinfold at about a 45-degree angle.[2]

Intramuscular Injections

Injection Site. Selection of the site of injection and needle size is based on the volume of vaccine to be administered, the thickness of the overlying subcutaneous tissue, the size of the muscle, and the desired depth below the muscle surface into which the material is to be injected. For most intramuscular injections, the quadriceps muscle mass in the anterolateral aspect of the upper thigh and the deltoid muscle of the upper arm are the preferred vaccination sites.[2, 7]

The quadriceps muscle mass in the anterolateral thigh is most commonly used for intramuscular injection in infants, whereas the upper arm is the usual recommended site for older children and adults.[12] After a child begins to walk, the upper arm is the preferred site.[12, 17] By this age, the child's deltoid muscle is usually large enough to be used for intramuscular injection. Although the anterolateral thigh is also an acceptable site, intramuscular injection into the thigh of 18-month-old children has been reported to cause transient limping.[12, 18, 19]

Because of the potential risk of injury to the sciatic nerve, the gluteal region is usually not recommended for routine vaccination.[2, 7, 20] This recommendation is primarily based on reported cases of sciatic nerve injury resulting from injection of antibiotics or antiserum into the buttocks.[12, 21–26] No reports of direct nerve injury resulting from gluteal injection of current childhood vaccines have been published.[27–29]

Because reports of sciatic nerve injury from intramuscular injection have involved administration of substances other than vaccines, some physicians continue to advocate the use of the gluteal region for routine vaccination.[30-32] When injections are given in the gluteal site, care must be taken to avoid nerve injury. The central region of the buttocks should be avoided. The needle should be inserted well into the upper, outer quadrant and directed anteriorly (i.e., not caudally or perpendicular to the skin surface). The ventrogluteal site (i.e., the center of the triangle bounded by the anterior superior iliac spine, the tubercle of the iliac crest, and the upper border of the greater trochanter of the femur) can also be used and is free of major neurovascular structures.[12] Because of the large volume that must be injected and the large muscle mass, the gluteal site is often used for passive immunization with immune globulin preparations.[7, 20]

• **Needle Size.** A 22- to 25-gauge needle is appropriate for the intramuscular administration of most vaccines. The ideal needle length may depend on the vaccination technique.[33] The technique recommended for intramuscular injections in the United States consists of gently bunching the muscle in the free hand while the needle is inserted to help minimize injury to nearby neurovascular structures and bone.[7, 33] However, the technique recommended by the World Health Organization (WHO) when using the anterolateral thigh consists of using the thumb and index finger to stretch the skin flat over the injection site while inserting the needle and injecting the vaccine.[33, 34]

The subcutaneous tissue and muscle layer thickness of the anterolateral thigh and deltoid region has been determined by ultrasonography.[33, 35, 36] On the basis of the resulting data, a ⅝-inch (16-mm) needle used according to the WHO technique is estimated to be adequate for intramuscular injection in the thigh of infants and toddlers and in the deltoid of toddlers.[33] However, using the technique recommended in the United States, a ⅞- to 1-inch (22- to 25-mm) needle would be necessary for adequate intramuscular penetration of the thigh of a 4-month-old infant and the thigh and deltoid of toddlers and older children.[2, 7, 33, 35]

For adolescents and adults, the ideal needle length for intramuscular injection depends on the weight and sex of the vaccinee. Poland and colleagues[36] reported that women have a greater deltoid fat pad thickness by ultrasonography and a greater deltoid skinfold thickness than men of an equal body mass index. These authors recommend a 1-inch (25-mm) needle for men for all weight ranges studied (i.e., 59 to 118 kg); for women, a ⅝-inch (16-mm) needle is indicated for those weighing less than 60 kg, a 1-inch (25-mm) needle is sufficient for those weighing 60 to 90 kg, and a 1½ inch (38-mm) needle is recommended for those weighing more than 90 kg.

Bleeding Disorders. Persons with bleeding disorders such as hemophilia can be at increased risk for bleeding after intramuscular injection. When hepatitis B or other vaccines recommended for intramuscular injection are indicated, vaccination can be scheduled shortly after administration of clotting factor replacement or similar therapy.[7] A 23-gauge or smaller needle can be used, and firm pressure without rubbing should be applied to the injection site for several minutes.[37] Alternatively, vaccines recommended for intramuscular injection might be administered subcutaneously to persons with a bleeding diathesis if the immune response and clinical reaction to these vaccines are generally expected to be comparable by either route of injection.[2, 7] An example is Hib (PRP-T) conjugate vaccine.[38-40]

Intradermal Injections

The deltoid region of the upper arm or the volar surface of the forearm is used for most intradermal injections.[2, 7, 20, 41] A ⅜- to ¼-inch, 25- to 27-gauge needle is recommended.[2, 7] The needle is inserted into the epidermis at an angle parallel to the long axis of the forearm. Care should be taken that the needle is inserted such that the entire bevel penetrates the skin and the injected solution raises a small bleb, thus demonstrating intradermal rather than subcutaneous injection of the vaccine. Because the amount of injected antigen is small, inadvertent subcutaneous injection may result in a suboptimal immunological response.[2, 7, 20] BCG vaccine is usually administered near the middle of the upper arm, over the insertion of the deltoid muscle.[41a]

Oral Administration

For vaccines given orally, the vaccine must be swallowed and retained. If a patient spits out, fails to swallow, or regurgitates a vaccine immediately after administration, the dose should be repeated.[2, 7, 42] Vomiting within 10 minutes is also a reason to readminister the dose of vaccine. If a second dose of the vaccine also is not retained, the dose should be readministered at a later date.[2, 7, 42]

Jet Injectors

Multiple-use nozzle jet injectors use the same nozzle tip to administer vaccine to multiple individuals. They have been used most frequently during mass vaccination campaigns and by the military to vaccinate large numbers of persons in a short time interval.[43-46]

These jet injectors have generally been considered safe and effective when they are used correctly by trained personnel. However, because the multiple-use nozzle of these jet injectors can become contaminated with blood or other infectious agents during use, the potential for patient-to-patient transmission of bloodborne pathogens exists and is a cause for serious concern.[47-53] The multiple-use nozzle jet injector that has been most widely used in the United States (Ped-O-Jet, Keystone Industries, Cherry Hill, NJ) has not been implicated in such transmission of bloodborne pathogens.[7, 44, 45, 54, 55] However, an outbreak of hepatitis B attributed to noncompliant use of another multiple-use nozzle jet injector (Med-E-Jet, Med-E-Jet Corporation, Cleveland, OH) has been reported.[56, 57]

The potential risk of disease transmission associated with multiple-use nozzle jet injectors would be greatest when vaccinating groups or populations in which the prevalence of hepatitis B virus, human immunodeficiency virus (HIV), or other bloodborne pathogens is expected to be high because of behavioral or other risk

factors.[58-60] Brito and coworkers[60] estimated the theoretical risk of patient-to-patient transmission of hepatitis B virus from use of a contaminated jet injector to be as high as 1 per 388 to 1 per 3367 injections in a population with a high seroprevalence of hepatitis B virus infection.

The potential risk of disease transmission can be minimized by effective training of healthcare workers on the proper care and use of jet injectors and by changing the injector tip or removing the jet injector from use until the nozzle is properly sterilized if contamination with blood or other body fluid is evident.[7] Swabbing the injector nozzle tip with alcohol or acetone between injections is recommended to reduce the risk of bloodborne disease transmission.[7, 61] However, results from one in vitro study of transmission of hepatitis B surface antigen (HBsAg) suggest that mechanical cleaning of a contaminated jet injector tip with a cotton ball moistened with acetone may reduce but not eliminate the potential risk of bloodborne disease transmission.[57]

Despite the potential risks, multiple-use nozzle jet injectors may be helpful for the rapid vaccination of large numbers of persons with the same vaccine when the use of needles and syringes is not practical. Public health authorities must assess whether the public health benefit from using a jet injector outweighs any potential risk of bloodborne disease transmission.[7] For example, because of the risks, the WHO no longer encourages the use of these jet injectors for mass vaccination campaigns.[62] To minimize vaccination-associated injury and disease, persons using jet injectors should be well trained in their use and maintenance. The manufacturer's guidelines for the use and maintenance of these devices should be strictly followed. Those with practical experience in the use of jet injectors, such as military recruit training centers, public health departments, and international organizations, can often advise on the use of these injectors in mass vaccination programs.

Unlike multiple-use nozzle jet injectors, recently developed jet injectors employ a single-use disposable nozzle.[62, 63, 63a] These needle-less jet injectors reduce the potential risk of bloodborne disease transmission both from vaccinee to vaccinee and from vaccinee to the person administering vaccine and thus are considered safer than either multiple-use nozzle jet injectors or needles with syringes.

ALLEVIATION OF PAIN AND DISCOMFORT ASSOCIATED WITH VACCINATION

Several methods have been reported to reduce the pain and discomfort associated with vaccination injection, but they have not been widely tested.[63a] Pretreatment with topical lidocaine-prilocaine emulsion 5% (Emla cream, Astra Pharmaceutical Products, Inc., Westborough, MA) can decrease the pain of diphtheria-tetanus-pertussis vaccination among infants by causing superficial anesthesia.[64] This cream is not licensed in the United States for use in infants younger than 1 month (i.e., neonates) or in infants younger than 12 months who are receiving treatment with methemoglobin-inducing agents because of a lack of safety data in neonates and concern about possible development of methemoglobinemia.[64, 64a, 65] Acetaminophen has been used in chil-

dren to reduce the discomfort and fever associated with vaccination.[66] However, acetaminophen can cause formation of methemoglobin and, thus, may interact with lidocaine-prilocaine cream if it is used concurrently.[64] Use of a topical refrigerant spray can reduce the short-term pain associated with injections and may be as effective as lidocaine-prilocaine cream.[67-69] Oral administration of sweet-tasting fluid just before injection may cause a calming or analgesic effect in some infants.[70] Distraction techniques such as listening to music or "blowing away pain" may also help children cope with the discomfort associated with vaccination.[71, 72]

The Z-track method of injection may also decrease the pain associated with intramuscular injection. Traction is applied to the skin and subcutaneous tissues prior to insertion of the needle and is released after injection. The injection track superficial to the muscle is thus displaced in relation to the track within the muscle, thereby preventing leakage of the vaccine from the muscle into the overlying tissues.

AGES FOR ADMINISTRATION OF IMMUNOBIOLOGICALS

Recommendations for the age and timing of vaccination are based on multiple factors, and childhood immunization schedules in various countries differ. Factors include the epidemiology and age-specific risks of contracting the naturally occurring disease, the age-specific risks of complications from the naturally occurring disease, the age-specific immunogenicity of the vaccine, the duration of immunity, and the schedule of recommended health visits. Ideally, a vaccine is recommended for the youngest age group at risk for the disease that is capable of an immunological response to the vaccine. These principles are exemplified by the following examples.

The optimal timing for administration of measles vaccine depends on both the rate of disappearance of passively acquired maternal antibody and the risk of exposure to measles virus. At birth and in the first 6 months of life, most infants have passive immunity to measles because of transplacentally acquired maternal measles antibodies. These antibodies interfere with the immune response to live virus measles vaccine by limiting vaccine virus replication. In many developing countries, where measles is highly endemic and frequently affects infants, routine measles vaccination is recommended at age 9 months.[2, 73] However, in the United States, where measles is less common and usually does not occur in infants, measles vaccine is routinely recommended at age 12 to 15 months.[2]

Another example is the recommended age of pertussis vaccination. Early infancy is the time of greatest risk of serious complications from naturally occurring pertussis, but infants who are younger than 1 month do not respond as well immunologically to pertussis vaccine as older infants do.[74-80] Initiation of routine immunization with pertussis vaccine is recommended at age 2 months.[81] This scheduling represents a compromise between factors affecting the immune response and the epidemiology of the disease necessitating early protection against pertussis.[79, 82, 83]

Vaccines[1] are listed under the routinely recommended ages. [Bars] indicate range of acceptable ages for immunization. Catch-up immunization should be done during any visit when feasible. Shaded (ovals) indicate vaccines to be assessed and given if necessary during the early adolescent visit.

Age ▶ / Vaccine ▼	Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	4-6 yrs	11-12 yrs	14-16 yrs
Hepatitis B[2,3]	Hep B-1									(Hep B)	
			Hep B-2		Hep B-3						
Diphtheria, Tetanus, Pertussis[4]			DTaP or DTP	DTaP or DTP	DTaP or DTP		DTaP or DTP[4]		DTaP or DTP	Td	
H. influenzae type b[5]			Hib	Hib	Hib	Hib					
Polio[6]			Polio[6]	Polio		Polio[6]			Polio		
Measles, Mumps Rubella[7]						MMR			MMR[7]	(MMR[7])	
Varicella[8]						Var				(Var[8])	

Approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

[1] This schedule indicates the recommended age for routine administration of currently licensed childhood vaccines. Combination vaccines may be used whenever any components of the combination is indicated and its other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

[2] Infants born to HBsAg-negative mothers should receive 2.5 µg of Merck vaccine (Recombivax HB®) or 10 µg of SmithKline Beecham (SB) vaccine (Engerix-B®). The 2nd dose should be administered at least 1 mo after the 1st dose. The 3rd dose should be given at least 2 mos after the second, but not before 6 mos of age.
Infants born to HBsAg-positive mothers should receive 0.5 mL hepatitis B immune globulin (HBIG) within 12 hrs of birth, and either 5 µg of Merck vaccine (Recombivax HB®) or 10 µg of SB vaccine (Engerix-B®) at a separate site. The 2nd dose is recommended at 1-2 mos of age and the 3rd dose at 6 mos of age.
Infants born to mothers whose HBsAg status is unknown should receive either 5 µg of Merck vaccine (Recombivax HB®) or 10 µg of SB vaccine (Engerix-B®) within 12 hrs of birth. The 2nd dose of vaccine is recommended at 1 to 2 mo of age and the 3rd dose at 6 mos of age. Blood should be drawn at the time of delivery to determine the mother's' HBsAg status; if it is positive, the infant should receive HBIG as soon as possible (no later than 1 wk of age). The dosage and timing of subsequent vaccine doses should be based upon the mother's HBsAg status.

[3] Children and adolescents who have not been vaccinated against hepatitis B in infancy may begin the series during any visit. Those who have not previously received 3 doses of hepatitis B vaccine should initiate or complete the series during the 11-12 year-old visit, and unvaccinated older adolescents should be vaccinated whenever possible. The 2nd dose should be administered at least 1 mo after the 1st dose, and the 3rd dose should be administered at least 4 mos after the 1st dose and at least 2 mos after the 2nd dose.

[4] DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the preferred vaccine for all doses in the vaccination series, including completion of the series in children who have received 1 or more doses of whole-cell DTP vaccine. Whole-cell DTP is an acceptable alternative to DTaP. The 4th dose (DTP or DTaP) may be administered as early as 12 mos of age, provided 6 mos have elapsed since the 3rd dose and if the child is unlikely to return at age 15-18 mos. Td (tetanus and diphtheria toxoids) is recommended at 11-12 years of age if at least 5 years have elapsed since the last dose of DTP, DTaP or DT. Subsequent routine Td boosters are recommended every 10 years.

[5] Three H. influenzae type b (Hib) conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® [Merck]) is administered at 2 and 4 mos of age, a dose at 6 mos is not required.

[6] Two poliovirus vaccines are currently licensed in the US: inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV). The following schedules are all acceptable to the ACIP, the AAP, and the AAFP. Parents and providers may choose among these options.
   1) 2 doses of IPV followed by 2 doses of OPV.
   2) 4 doses of IPV.
   3) 4 doses of OPV.   ·
The ACIP recommends 2 doses of IPV at 2 and 4 mos of age followed by 2 doses of OPV at 12-18 mos and 4-6 years of age. IPV is the only poliovirus vaccine recommended for immunocompromised persons and their household contacts.

[7] The 2nd dose of MMR is recommended routinely at 4-6 yrs of age but may be administered during any visit, provided at least 1 mo has elapsed since receipt of the 1st dose and that both doses are administered beginning at or after 12 mos of age. Those who have not previously received the second dose should complete the schedule no later than the 11-12 year visit.

[8] Susceptible children may receive Varicella vaccine (Var) at any visit after the first birthday, and those who lack a reliable history of chickenpox should be immunized during the 11-12 year-old visit. Susceptible children 13 years of age or older should receive 2 doses, at least 1 month apart.

Figure 5-1. Recommended childhood immunization schedule, United States, January–December 1998.

Vaccination too early in life may also affect the immune response to subsequent doses of vaccine. For example, neonatal administration of diphtheria and tetanus toxoids may result in the suppression of antibody responses to subsequent doses of Hib conjugate vaccines.[84] When children who receive measles vaccine before the age of 1 year are revaccinated, they develop vaccine-induced immunity against disease but may have a somewhat diminished antibody response compared with children vaccinated initially after their first birthday.[85]

Current immunization schedules in the United States are given in Figure 5–1 and Table 5–3.[2, 86] The minimum ages for initial administration of childhood vaccines and minimum acceptable intervals between doses in the United States are listed in Table 5–4. Other immunization schedules are discussed in Chapters 42 to 44.

SPACING OF VACCINE DOSES
Nonsimultaneous Administration of the Same Vaccine

Although administration of one dose of some vaccines usually induces a protective antibody response, many other vaccines require the administration of multiple doses in a primary series for development of immunity. Examples of the former are rubella, yellow fever, and pneumococcal vaccines; examples of the latter are poliovirus, hepatitis B, and pertussis vaccines. In addition, periodic revaccination with certain vaccines may be necessary to maintain immunity. Examples are yellow fever and pertussis vaccines and tetanus and diphtheria toxoids. Table 5–4 lists recommended minimum intervals between doses of the same vaccine.

Because of immunological memory, longer than routinely recommended intervals between doses do not impair the immunological response to live and killed vaccines that require more than one dose to achieve primary immunity.[2, 7] Similarly, delayed administration of recommended booster doses does not adversely affect the antibody response to such doses.[2, 7] Thus, the interruption of a recommended primary series or an extended lapse between booster doses does not necessitate reinitiation of the entire vaccination series.[2, 7] For example, lengthening the interval between two doses of inactivated poliovirus vaccine (IPV) may actually increase the antibody response to the second dose.[87–89] In the case of oral

Table 5–3. RECOMMENDED IMMUNIZATION SCHEDULES FOR CHILDREN NOT IMMUNIZED IN THE FIRST YEAR OF LIFE*

RECOMMENDED TIME/AGE	IMMUNIZATION†‡	COMMENTS
Younger than 7 Years		
First visit	DTaP (or DTP), Hib, HBV, MMR, OPV¶	If indicated, tuberculin testing may be done at the same visit.
		If child is 5 yr of age or older, Hib is not indicated in most circumstances.
Interval after first visit		
1 mo (4 wk)	DTaP (or DTP), HBV, Var**	The second dose of OPV may be given if accelerated poliomyelitis vaccination is necessary, such as for travelers to areas where polio is endemic.
2 mo	DTaP (or DTP), Hib, OPV¶	Second dose of Hib is indicated only if the first dose was received when younger than 15 mo.
≥8 mo	DTaP (or DTP), HBV, OPV¶	OPV and HBV are not given if the third doses were given earlier.
Age 4–6 yr (at or before school entry)	DTaP (or DTP), OPV,¶ MMR††	DTaP (or DTP) is not necessary if the fourth dose was given after the fourth birthday; OPV is not necessary if the third dose was given after the fourth birthday.
Age 11–12 yr	See Figure 5–1	
7–12 Years		
First visit	HBV, MMR, Td, OPV¶	
Interval after first visit		
2 mo (8 wk)	HBV, MMR,†† Var,** Td, OPV¶	OPV may also be given 1 mo after the first visit if accelerated poliomyelitis vaccination is necessary.
8–14 mo	HBV,‡‡ Td, OPV¶	OPV is not given if the third dose was given earlier.
Age 11–12 yr	See Figure 5–1	

*The table is not completely consistent with all package inserts. For products used, also consult manufacturer's package insert for instructions on storage, handling, dosage, and administration. Biologicals prepared by different manufacturers may vary, and package inserts of the same manufacturer may change from time to time. Therefore, the physician should be aware of the contents of the current package insert.

†If all needed vaccines cannot be administered simultaneously, priority should be given to protecting the child against those diseases that pose the greatest immediate risk. In the United States, these diseases for children younger than 2 years are usually measles and *Haemophilus influenzae* type b infection; for children older than 7 years, they are measles, mumps, and rubella. Before 13 years of age, immunity against hepatitis B and varicella should be ensured.

‡DTaP, HBV, Hib, MMR, and Var can be given simultaneously at separate sites if failure of the patient to return for future immunizations is a concern.

¶IPV is also acceptable. However, for infants and children starting vaccination late (i.e., after 6 months of age), OPV is preferred to complete an accelerated schedule with a minimum number of injections.

**Varicella vaccine can be administered to susceptible children any time after 12 months of age. Unvaccinated children who lack a reliable history of chickenpox should be vaccinated before their 13th birthday.

††Minimal interval between doses of MMR is 1 month (4 weeks).

‡‡HBV may be given earlier in a 0-, 2-, and 4-month schedule.

HBV, hepatitis B virus vaccine; Var, varicella vaccine; DTP, diphtheria and tetanus toxoids and pertussis vaccine; DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; Hib, *Haemophilus influenzae* type b conjugate vaccine; OPV, oral poliovirus vaccine; IPV, inactivated poliovirus vaccine; MMR, live measles-mumps-rubella vaccine; Td, adult tetanus toxoid (full dose) and diphtheria toxoid (reduced dose), for children 7 years of age and older and adults.

Adapted from American Academy of Pediatrics. Active immunization. In Peter G (ed). 1997 Red Book: Report of the Committee on Infectious Diseases (24th ed). Elk Grove Village, IL, American Academy of Pediatrics, 1997, p 20.

Table 5–4. MINIMUM AGE FOR INITIAL VACCINATION AND MINIMUM INTERVAL BETWEEN VACCINE DOSES, BY TYPE OF VACCINE

VACCINE	MINIMUM AGE FOR FIRST DOSE*	MINIMUM INTERVAL FROM DOSE 1 TO 2*	MINIMUM INTERVAL FROM DOSE 2 TO 3*	MINIMUM INTERVAL FROM DOSE 3 TO 4*
DTaP/DTP (DT)†	6 wk	4 wk	4 wk	6 mo
Hib (primary series)				
HbOC	6 wk	4 wk	4 wk	‡
PRP-T	6 wk	4 wk	4 wk	‡
PRP-OMP	6 wk	4 wk	‡	
Hib-DTP combination	6 wk	4 wk	4 wk	6 mo
Hepatitis B	Birth	4 wk	8 wk§	
Poliovirus				
IPV/OPV sequential	6 wk	4 wk	4 wk	4 wk
OPV only	6 wk	4 wk	4 wk	¶
IPV only	6 wk	4 wk	8 wk‖	¶
Measles-mumps-rubella	12 mo**	4 wk		
Varicella	12 mo	4 wk††		

*These minimum acceptable ages and intervals may not correspond with the *optimal* ages and intervals for vaccination recommended by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the vaccine manufacturer. Four weeks is considered to be 28 days.

†The total number of doses of diphtheria and tetanus toxoids should not exceed six each before the seventh birthday. Children who have received all four primary vaccination doses before their fourth birthday should receive a fifth dose at 4 to 6 years of age (i.e., before entering kindergarten or elementary school) *and* at least 6 months after the fourth dose.

‡The booster dose of Hib vaccine, which is recommended after the primary vaccination series, should be administered no earlier than 12 months of age *and* at least 2 months after the previous dose of Hib vaccine.

§This final dose is recommended at least 4 months after the first dose and no earlier than 6 months of age.

¶If the third dose is administered on or after the fourth birthday, the fourth dose is not required.

‖The preferred interval between the second and third doses of IPV is at least 6 months. If accelerated protection is needed because of increased risk of exposure to poliovirus (e.g., due to international travel), the interval between the second and third dose of IPV can be 4 weeks.

**Although the age for measles vaccination may be as young as 6 months in outbreak areas, where cases are occurring in children who are younger than 1 year, children initially vaccinated before the first birthday should be revaccinated at 12 to 15 months of age, and an additional dose of vaccine should be administered at the time of school entry or according to local policy. Doses of measles-mumps-rubella vaccine or other measles-containing vaccines should be separated by at least 4 weeks.

††Two doses of varicella vaccine are recommended only for people 13 years and older.

DT, diphtheria and tetanus toxoids vaccine; HbOC, *H. influenzae* oligosaccharide conjugate; PRP-T, polyribosylribitol phosphate–tetanus toxoid vaccine; PRP-OMP, polyribosylribitol phosphate outer membrane protein conjugate.

typhoid (Ty21a) vaccine, an exception has been proposed. Specifically, if the primary vaccination series is interrupted for longer than 3 weeks, the primary series should be started again (see Chapter 33).

Administration of doses of a vaccine at shorter intervals than recommended may result in a reduced immune response with diminished vaccine efficacy and should be avoided[2, 7] (see Table 5–4). Multiple doses of some live vaccines are recommended to stimulate an immune response to different types of the same virus, such as poliovirus types 1, 2, and 3, or to induce immunity in persons who failed to mount an immune response to an earlier dose of vaccine, such as measles.[42, 90] These multiple doses constitute a primary vaccination series and are not "booster doses."

Guidelines for spacing the administration of different vaccines are given in Table 5–5. The theoretical possibility that two doses of the same or different live virus vaccines administered within too short an interval may inhibit the immunological response to the second dose is based on evidence from both animal and human studies.[91-94] Although the potential for immune interference is the reason for the recommendation that doses of live virus vaccines not administered at the same time should be separated by at least 4 weeks, the biological reason for such interference is not known. Petralli and colleagues[93, 94] reported that the immune response to smallpox vaccination was affected by prior administration of live attenuated measles vaccine, and interferon produced in response to the initial dose of live virus vaccine has been postulated to inhibit replication of

vaccine virus in the subsequent vaccine dose. Such interference remains theoretical and has not been reported between doses of currently licensed live virus vaccines. In addition, multiple studies have demonstrated that previous or intercurrent viral illness in a vaccinee does not appear to interfere with the immune response to live virus vaccines.[95-100] Such interference might be expected on the basis of the findings of Petralli and colleagues.[93, 94] These inconsistencies suggest that the question of interference between live virus vaccines should be re-examined.

Table 5–5. GUIDELINES FOR SPACING THE ADMINISTRATION OF KILLED AND LIVE ANTIGENS

ANTIGEN COMBINATION	RECOMMENDED MINIMUM INTERVAL BETWEEN DOSES
≥2 Killed antigens	None; may be given simultaneously or at any interval between doses
Killed and live antigens	None; may be given simultaneously or at any interval between doses (*exception: cholera and yellow fever vaccines**)
≥2 Live antigens	4 wk, if not administered simultaneously (*exception: oral poliovirus vaccine can be administered at any time before, with, or after measles-mumps-rubella and oral typhoid vaccines*)

*If time permits, cholera and yellow fever vaccines should not be administered simultaneously with each other; at least 3 weeks should elapse between administration of these vaccines. If these two vaccines must be administered simultaneously or within 3 weeks of each other, the antibody response may not be optimal.

Too frequent administration of some killed vaccines such as tetanus toxoid can result in increased rates of reactions in some vaccinees.[2, 101–103] Such reactions probably result from the formation of circulating antigen-antibody complexes.[2, 104–107]

Simultaneous Administration of Different Vaccines

Simultaneous administration of all indicated vaccines is an essential component of childhood vaccination programs.[2, 7] Simultaneous administration of different vaccines is also particularly important when return of the recipient for further vaccination is questioned, when imminent exposure to several vaccine-preventable diseases is expected, or when preparing for international travel on short notice. Unless specifically licensed for injection in the same syringe, different vaccines administered simultaneously should be injected separately and at different anatomical sites. If both upper and lower limbs must be used for simultaneous administration of different vaccines, the anterolateral thigh is often chosen for intramuscular injections and the deltoid region for subcutaneous injections. If more than one injection must be administered in a single limb, the thigh is usually preferred because of its large muscle mass. The distance separating two injections in the same limb should be sufficient (e.g., 1 to 2 inches) to minimize the chance of overlapping local reactions.[17, 18] In general, different vaccines, including live virus products, can be administered simultaneously without reducing their safety and effectiveness[108] (see Table 5–5). Studies of cortisol levels and behavioral responses of infants to vaccination indicate that responses are similar in infants who receive two inoculations during one visit and infants who receive a single inoculation, suggesting that a second injection does not increase stress.[109, 110]

Whereas simultaneous administration of vaccines associated with frequent local or systemic reactions could result in accentuation of these reactions, increased severity or incidence of adverse reactions has not been observed after simultaneous administration of the most widely used vaccines.[7] Similarly, simultaneous administration of vaccines does not generally cause immunological interference.[108] An exception is concurrent administration of yellow fever and cholera vaccines.[111, 112]

Nonsimultaneous Administration of Different Vaccines

With the exception of two live virus vaccines administered within an interval of 4 weeks of each other, vaccines can generally be administered at any time before or after a different vaccine[2, 7] (see Table 5–5). As previously noted, the immune response to a live virus vaccine theoretically might be impaired if it is administered nonsimultaneously within 4 weeks after another live virus vaccine.[93, 94] Whereas interference has not been observed for currently available live virus vaccines in the United States, to minimize the theoretical possibility of interfer-

ence, live virus vaccines not administered at the same time should generally be separated by at least 4 weeks.[2, 7] However, OPV and MMR vaccines can be administered at any interval before or after each other.

INTERFERENCE BY IMMUNE GLOBULINS

Passively acquired antibodies can interfere with the immune response to certain vaccines, both live and inactivated, and toxoids. The result can be either the absence of seroconversion or a blunting of the immune response with lower final antibody concentrations in the vaccinee. Passively acquired antibody, however, does not affect the immune response to all vaccines.

Interference with Live Vaccines

To elicit an adequate immune response, live vaccine virus must replicate within the recipient. The probable mechanism by which passively acquired immune globulin blunts the immune response to live virus vaccines is by neutralization of vaccine virus resulting in inhibition of viral replication and insufficient antigenic mass.[113] For example, persisting transplacentally acquired maternal measles antibodies inhibit the response to live measles vaccine in infants for as long as 12 months and perhaps longer.[114–116] The age to which inhibition persists has been correlated with concentrations of maternal or cord blood antibodies.[117–119] Rubella vaccine virus may be less susceptible than measles vaccine virus to these transplacentally acquired maternal antibodies.[120]

Intramuscular or intravenous administration of immune globulin–containing preparations (e.g., serum immune globulin, hyperimmune globulins, intravenous immune globulin, and blood) before or simultaneous with certain vaccines can also affect the immune response to live virus vaccines. When partially attenuated Edmonston B measles vaccine, which is no longer used in the United States, was administered concurrently with measles immune globulin in an effort to reduce the incidence of adverse events associated with this vaccine, the rate of seroconversion was not affected but the geometric mean titer of serum measles antibody was diminished.[121–123] In one study, children who received an investigational bacterial polysaccharide immune globulin (BPIG) intramuscularly had a reduced immune response to live measles vaccine for as long as 5 months after receipt of BPIG.[124] The measles antibody seroconversion rate and geometric mean titer were lower among the children who received BPIG compared with those who received placebo. Blunting of the immune response to live rubella vaccine also occurred after receipt of BPIG but was less marked and of shorter duration.[124]

Although passively acquired antibodies can interfere with the response to rubella vaccine, the low doses of anti-Rh(D) globulin administered to postpartum women have not been demonstrated to inhibit the immune response to RA27/3 strain rubella vaccine.[125] Parenterally administered immune globulin preparations also do not appear to adversely affect the immune response to yel-

low fever vaccine.[126] Although high concentrations of passively acquired-antibodies may reduce the serum antibody response to live poliovirus vaccine, they have little effect on the replication of vaccine virus and development of gastrointestinal tract immunity.[79, 126-128] Data are insufficient to determine the extent to which passively acquired antibodies interfere with the immune response to other live viral or bacterial vaccines, such as varicella, mumps, and typhoid (Ty21a strain).[129]

Interference with Inactivated (Killed) Vaccines

Interference with current inactivated and component vaccines is less marked than with live vaccines and requires exposure to large doses of passively acquired antibodies.[79, 128, 130, 131] The mechanism by which passively acquired antibodies interfere with the immunological response of inactivated and toxoid vaccines is not clear. Moderate doses of parenterally administered immune globulins have not inhibited the development of a protective immune response to diphtheria and tetanus toxoids and pertussis vaccine (DTP), tetanus toxoid, hepatitis B vaccines, Hib conjugate vaccines, and rabies vaccines.[131-133] For example, although the concurrent administration of inactivated hepatitis A vaccine and immune globulin can result in lower serum antibody concentrations than if vaccine alone is administered, seroconversion rates have not been diminished.[2, 134-136] In another study, infants with high concentrations of passively acquired maternal antibody to hepatitis A virus had seroconversion rates similar to those of vaccinated infants without maternal antibodies but lower serum antibody concentrations after receipt of hepatitis A vaccine.[137] Further studies are under way to determine if these findings are of clinical significance.

The manufacturer of respiratory syncytial virus immune globulin, intravenous (RSV-IGIV) has suggested that an additional dose of certain inactivated vaccines (i.e., diphtheria, tetanus, and acellular pertussis vaccine [DTaP]; DTP; Hib; and OPV) may be necessary to ensure a protective immune response from these vaccines in recipients of RSV-IGIV (RespiGam package insert). However, currently available data are inconclusive and do not support a recommendation for additional doses of these vaccines.[138]

Recommendations for Spacing Administration of Vaccines and Immune Globulins

Interference of immune globulins with the immune response to vaccines is dose related and, therefore, more likely to occur and to persist for a longer period after receipt of larger doses of immune globulins.[124, 139] The recommended interval between administration of immune globulin preparations and vaccines is based on the following considerations: (1) whether evidence suggests interference between immune globulin and the vaccine; (2) the dose of the immune globulin administered; and (3) the expected half-life of immunoglobulin G. Recommended intervals between administration of immune globulin preparations and various live and killed vaccines are listed in Tables 5-6 and 5-7.

Table 5-6. GUIDELINES FOR SPACING THE ADMINISTRATION OF IMMUNE GLOBULIN PREPARATIONS* AND VACCINES

SIMULTANEOUS ADMINISTRATION

Immunobiological Combination	Recommended Minimum Interval Between Doses
Immune globulin and killed antigen	None; may be administered simultaneously at different sites or at any time between doses
Immune globulin and live antigen	Should generally not be administered simultaneously (*exception: oral poliovirus vaccine, yellow fever vaccine, and oral typhoid [Ty21a] vaccine can be administered at any time before, after, or simultaneous with an immune globulin preparation*) If simultaneous administration of measles-mumps-rubella vaccine or its component vaccines or varicella vaccine in unavoidable, administer at different sites and test for seroconversion or revaccinate after the recommended interval.†

NONSIMULTANEOUS ADMINISTRATION

Immunobiological Administered		Recommended Minimum Interval Between Administration of Immune Globulin Preparations and Vaccine Antigens	
First	*Second*	*Interval*	*Antigen*
Immune globulin	Killed antigen	None	
Killed antigen	Immune globulin	None	
Immune globulin	Live antigen	None	Oral poliovirus, yellow fever, oral typhoid (Ty21a)
		3 mo	Rubella, mumps
		5 mo	Varicella
		Dose related†	Measles
Live antigen	Immune globulin	2 wk	Measles, rubella, mumps
		3 wk	Varicella

*Blood products containing large amounts of immune globulin (e.g., serum immune globulin, specific immune globulins, immune globulin [intravenous], whole blood, packed red blood cells, plasma, or platelet products).

†Rubella and mumps vaccines, 3 months; varicella vaccine, 5 months; measles-containing vaccines, dose related. See Table 5-7.

Table 5-7. SUGGESTED INTERVALS BETWEEN ADMINISTRATION OF IMMUNE GLOBULIN PREPARATIONS FOR VARIOUS INDICATIONS AND VACCINES CONTAINING LIVE MEASLES VIRUS*

INDICATIONS	DOSE (mg IgG/kg)	TIME INTERVAL (mo) BEFORE MEASLES VACCINATION
Tetanus prophylaxis (TIG)	250 units (10 mg IgG/kg) IM	3
Hepatitis A prophylaxis (IG)		
Contact prophylaxis	0.02 mL/kg (3.3 mg IgG/kg) IM	3
International travel	0.06 mL/kg (10 mg IgG/kg) IM	3
Hepatitis B prophylaxis (HBIG)	0.06 mL/kg (10 mg IgG/kg) IM	3
Rabies prophylaxis (HRIG)	20 IU/kg (22 mg IgG/kg) IM	4
Varicella prophylaxis (VZIG)	125 units/10 kg (20–40 mg IgG/kg) IM (maximum, 625 units)	5
Measles prophylaxis (IG)		
Standard (i.e., nonimmunocompromised contact)	0.25 mL/kg (40 mg IgG/kg) IM	5
Immunocompromised contact	0.50 mL/kg (80 mg IgG/kg) IM	6
Blood transfusion		
RBCs, washed	10 mL/kg (negligible IgG/kg) IV	0
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3
Packed RBCs (Hct 65%)†	10 mL/kg (60 mg IgG/kg) IV	6
Whole blood (Hct 35–50%)†	10 mL/kg (80–100 mg IgG/kg) IV	6
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7
Replacement therapy for immune deficiencies	300–400 mg/kg IV‡ (as IGIV)	8
Respiratory syncytial virus prophylaxis	750 mg/kg IV (as RSV-IGIV)	9
Treatment of		
Immune thrombocytopenic purpura	400 mg/kg IV (as IGIV)	8
	1000 mg/kg IV (as IGIV)	10
Kawasaki disease	2 g/kg IV (as IGIV)	11

*This table is not intended for determining the correct indications and dosage for the use of immune globulin preparations. Unvaccinated persons may not be fully protected against measles during the entire suggested time interval, and additional doses of immune globulin or measles vaccine may be indicated after measles exposure. The concentration of measles antibody in a particular immune globulin preparation can vary by lot. The rate of antibody clearance after receipt of an immune globulin preparation can also vary. The recommended time intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

†Assumes a serum IgG concentration of 16 mg/mL.

‡Measles vaccination is recommended for human immunodeficiency virus–infected children who do not have evidence of severe immunosuppression, but it is contraindicated for patients who have congenital disorders of the immune system.

HBIG, hepatitis B immune globulin; Hct, hematocrit; HRIG, human rabies immune globulin; IG, serum immune globulin; IGIV, immune globulin, intravenous; IM, intramuscularly; IV, intravenously; RBCs, red blood cells; RSV-IGIV, respiratory syncytial virus immune globulin, intravenous; TIG, tetanus immune globulin; VZIG, varicella-zoster immune globulin.

In the United States, killed (i.e., inactivated) vaccines may be administered simultaneously with or at any time before or after receipt of an immune globulin preparation.[2,7,20] The vaccine and immune globulin preparation should be administered at different sites, and the standard recommended doses of the corresponding vaccines should be used.[2,7] Supplementary doses are not indicated.

Recommendations for administration of live virus vaccines vary on the basis of the aforementioned considerations. After receipt of an immune globulin preparation or other blood product, measles vaccine should be deferred during the intervals listed in Table 5-7.[128,140] Immune globulin preparations also contain rubella, mumps, and varicella antibodies. Because high doses of passively acquired antibodies can inhibit the immune response to live rubella vaccine for as long as 3 months, administration of rubella vaccine should be postponed for at least 3 months after receipt of an immune globulin preparation or blood product.[7,124,141] Although the effect of immune globulin preparations on the response to live mumps and live varicella vaccines has not been defined, postponement of administration of mumps and varicella vaccines for 3 months and 5 months, respectively, after receipt of an immune globulin preparation is recommended because of possible interference.[7,142-144]

Immune globulin preparations administered too soon after vaccination with MMR or varicella vaccines can interfere with the immune response. Therefore, according to current guidelines, if administration of an immune globulin preparation becomes necessary less than 2 weeks after receipt of MMR or its component vaccines or less than 3 weeks after receipt of varicella vaccine, readministration of the vaccine is recommended after the appropriate interval listed in Tables 5-6 and 5-7, unless serological testing indicates that a protective antibody response already occurred.[7,140,144] For example, if an immune globulin preparation is administered less than 3 weeks after receipt of varicella vaccine, vaccine should be readministered at least 5 months after the

immune globulin preparation unless serological testing indicates an adequate immune response to the initial dose of varicella vaccine.

Because the immune response to OPV and yellow fever vaccines is not adversely affected by immune globulin preparations, these vaccines can be administered at any time in relation to the receipt of immune globulin preparations.[126] Live oral typhoid (Ty21a) vaccine is also recommended for administration at any time in relation to receipt of immune globulin preparations.[7, 15]

INTERCHANGEABILITY OF VACCINES OF DIFFERENT MANUFACTURERS

Combination and monovalent vaccines against the same diseases with similar antigens and produced by the same manufacturer are considered interchangeable in most situations.[2, 7] However, supporting data on the safety, immunogenicity, and efficacy of using comparable vaccines from different manufacturers for different doses of a vaccination series are frequently limited or unavailable. When the same vaccine cannot be used to complete an immunization series, similar vaccines produced by different manufacturers or produced by the same manufacturer in different countries have generally been considered acceptable to complete the immunization series as long as each vaccine is used as licensed and recommended.[2, 7]

Some diseases have serological correlates of immunity that can be used to evaluate vaccine interchangeability. For example, in studies in which one or more doses of hepatitis B vaccine produced by one manufacturer were followed by doses from another manufacturer, the immune response was comparable to that resulting from use of a single vaccine type.[145, 146] Whereas Hib conjugate vaccines differ in antigen composition, interchangeability of different products has been validated on the basis of the accepted serological correlate of immunity against *H. influenzae* type b invasive disease.[147-149]

Determination of vaccine interchangeability is more difficult for diseases without serological correlates of immunity. For example, in the absence of such a correlate for *Bordetella pertussis* infection, the interchangeability of acellular pertussis vaccines is difficult to assess. Thus, when feasible, acellular pertussis vaccine from the same manufacturer is preferred for the entire primary vaccination series.[2, 150] However, if this regimen is not feasible, any of the licensed products can be used to continue or complete the series.[2, 150]

HYPERSENSITIVITY TO VACCINE COMPONENTS

Types of Reactions

Hypersensitivity reactions after vaccination can be local or systemic. They can vary in severity from mild discomfort at the site of vaccination to severe anaphylaxis. Onset can be either immediate or delayed. Serious reactions are rare. Whether a specific hypersensitivity reaction is caused by a vaccine component or an unrelated environmental allergen can be difficult to determine. However, symptoms occurring immediately after vaccination that are suggestive of an anaphylactic reaction contraindicate further administration of that vaccine to the recipient.[2, 7]

Urticaria and anaphylactic reactions have been reported after the administration of DTP, diphtheria and tetanus toxoids (DT, Td), and tetanus toxoid.[151-153] Whereas immunoglobulin E–type antibodies to tetanus and diphtheria antigens have been identified in some patients with these symptoms, transient urticarial rashes are not a contraindication to subsequent vaccination, because they are unlikely to be anaphylactic unless they appear within minutes after vaccination.[2, 154-156] A serum sickness–type reaction caused by circulating complexes of vaccine antigen and previously acquired antibody is the likely cause of these reactions, and subsequent vaccination is unlikely to result in the necessary ratio of antigen to antibody concentration to form immune complexes.[154, 157]

Tetanus toxoid is contraindicated in persons who experienced an immediate anaphylactic reaction to tetanus toxoid–containing vaccine, unless the person can be desensitized to the toxoid.[2] Because of the importance of tetanus immunization and the uncertainty about which vaccine component might be the cause of the reaction, the patient may be referred to an allergist for evaluation and possible desensitization.[154, 158-161] On occasion, a history of a prior allergic reaction to tetanus vaccine may refer to a reaction to tetanus antiserum of equine origin that was used for tetanus prophylaxis before human-derived tetanus immune globulin became available in the 1960s. Thus, before use of tetanus toxoid is discontinued because of an alleged episode of anaphylaxis, skin testing and possible desensitization should be considered.[158, 159]

Local or systemic reactions, such as redness and soreness at the vaccination site and fever, have been associated with receipt of DTP, plague, cholera, and inactivated whole-cell typhoid vaccines.[107, 162-166] Such reactions are usually caused by a toxin in the vaccine rather than by hypersensitivity to a specific component.[7]

With some vaccines, such as Japanese encephalitis, immediate or delayed onset of generalized urticaria and angioedema that can progress to respiratory distress and hypotension has been reported after vaccination.[167-169] The pathogenesis of these reactions is not known.

Vaccine Components Causing Hypersensitivity

Proteins

Egg protein is a constituent of vaccines prepared with use of embryonated chicken eggs. Examples include influenza, yellow fever, measles, and mumps vaccines. On rare occasions, these vaccines can induce anaphylaxis or other immediate hypersensitivity reactions, and these reactions are sometimes attributed to egg protein antigen.[2, 5, 90, 170-175] As a result, some of these vaccines are

contraindicated in persons with a history of anaphylactic reactions to egg ingestion unless desensitization has been successfully completed.[2, 5, 170, 171, 173, 176] For example, persons needing yellow fever vaccine who have a history of systemic anaphylactic-like symptoms (e.g., generalized urticaria, wheezing, and hypotension) after egg ingestion can be skin tested with yellow fever vaccine before vaccination and desensitized.[2, 5, 170] Although available, skin testing and desensitization with influenza vaccine are often precluded by the risk of reactions, the need for yearly vaccination, and the availability of chemoprophylaxis against influenza A with amantadine or rimantadine.[2, 171, 176, 177]

Although measles and mumps vaccines are produced by use of chick embryo fibroblast cell culture, persons with hypersensitivity to eggs are at low risk for anaphylactic reactions to these vaccines, and skin testing with vaccine is not predictive of allergic reaction after immunization.[2, 178-180] Therefore, neither skin testing nor administration of gradually increasing doses of vaccine is required when these vaccines are administered to persons who are allergic to eggs.[2, 90, 140, 142]

Live virus vaccines, such as measles, mumps, rubella, yellow fever, and varicella, contain gelatin as a stabilizer. Persons with a history of allergy to gelatin have rarely experienced an anaphylactic reaction after vaccination with such a vaccine.[181-183] Skin testing of persons with a history of systemic anaphylactic-like symptoms after gelatin ingestion may be useful to identify those at risk for severe hypersensitivity reactions to vaccination, but no protocol for such testing or desensitization has been published. Because gelatin used as a vaccine stabilizer may be of porcine origin whereas ingested food gelatin may be of bovine origin, the absence of a history of allergy to gelatin-containing foods does not eliminate the possibility of a gelatin-mediated reaction to vaccine.

Approximately 6% of persons who receive a booster dose of human diploid rabies vaccine develop a serum sickness–type illness.[184, 185] This reaction is thought to be caused by sensitization to human albumin that has been altered chemically by a virus-inactivating agent used in the production of the vaccine.[2, 186]

Antibiotics

Live virus vaccines frequently contain trace amounts of one or more antibiotics such as neomycin, streptomycin, and polymyxin B. Vaccine contents are listed in the manufacturer's product label for each vaccine. The most common allergic response to neomycin is a delayed-type (cell-mediated) local contact dermatitis consisting of an erythematous, pruritic papule that occurs 48 to 96 hours after vaccine administration.[2, 7, 187] Such delayed-type reactions are not contraindications for vaccination.[2, 7, 187, 188] However, persons who have experienced an anaphylactic reaction to neomycin or to another antibiotic vaccine constituent should not receive vaccines containing that antibiotic.[2, 90, 189, 190] No vaccines currently licensed in the United States contain penicillin or penicillin derivatives.

Mercury Compounds

Mercury hypersensitivity may be rarely elicited after receipt of vaccines containing the preservative thimerosal.[191-193] Many vaccines produced in the United States, such as diphtheria, tetanus, pertussis, hepatitis B, influenza, and Japanese encephalitis, contain this preservative. However, most patients do not react adversely to thimerosal as a vaccine component even if patch or intradermal skin test responses are positive.[194] Furthermore, hypersensitivity to this compound usually consists of local delayed-type reactions, and mercury hypersensitivity is not a contraindication to vaccinations.[2, 7, 159, 195, 196]

Recommended Management of Acute Vaccine Reactions

Although it is extremely rare after immunization, the immediate onset and life-threatening nature of an anaphylactic reaction require that personnel and facilities providing vaccination be capable of providing initial care for suspected anaphylaxis. Epinephrine and equipment for maintaining an airway should be available for immediate use.

Anaphylaxis usually begins within several minutes of administration of vaccine. Rapid recognition and initiation of treatment are required to prevent possible progression to cardiovascular collapse. If flushing, facial edema, urticaria, itching, swelling of the mouth or throat, wheezing, difficulty breathing, or other signs of anaphylaxis occur, the patient should be placed in a recumbent position with the legs elevated. Aqueous epinephrine (1:1000) should be administered and may be repeated within 10 to 20 minutes.[197] A dose of diphenhydramine hydrochloride may shorten the reaction, but it will have little immediate effect. Maintenance of any airway and oxygen administration may be necessary. Arrangements should be made for immediate transfer to an emergency facility for further evaluation and treatment. All patients should be observed for at least 12 hours after the onset of symptoms.[197]

Postvaccination syncope, unrelated to anaphylactic hypersensitivity, can also occur. In a report of 697 cases of syncope after vaccination, six patients suffered skull fracture, cerebral bleeding, or cerebral contusion from falls.[198] In this same study, almost 90% of the cases of syncope occurred within 15 minutes or less of vaccination, and 98% of cases occurred within 30 minutes. Because of the small risk of an anaphylactic reaction and the unrelated risk of postvaccination syncope, the AAP recommends observation for 15 to 20 minutes after immunization whenever possible.[2]

VACCINATION OF PRETERM INFANTS

The immune response to vaccination is a function of postnatal age rather than of gestational age.[199-202] Transplacentally acquired maternal antibody is present

at lower concentrations and, thus, persists for a shorter interval in preterm infants than in gestationally mature infants.[201, 203-205] Because they have less transplacentally acquired maternal antibody, inhibition of the immune response in premature infants may be less than in full-term infants.[201, 206]

DTP, OPV, IPV, and Hib vaccines are generally immunogenic and safe for preterm infants when vaccination is initiated at the same chronological age (i.e., approximately 2 months) and administered according to the same routine schedule as for full-term infants.[207-218] However, some studies also suggest that the immune response to certain vaccines may be impaired when vaccination of extremely premature infants or those of very low birth weight is initiated at the usual time.[212, 213, 219-223] For example, D'Angio and colleagues[212] reported that a similar proportion of extremely premature infants (i.e., less than 29 weeks' gestation and birth weight less than 1000 g) and full-term infants had protective antibody concentrations to tetanus toxoid, Hib, and poliovirus serotypes 1 and 2 after a vaccination series of three doses of DTP and Hib vaccines and two doses of poliovirus vaccine (i.e., IPV followed by OPV) initiated at a chronological age of 2 months. However, the preterm infants were less likely to have detectable antibody to poliovirus serotype 3. Protective antibody titers were still present when the children were retested at 3 to 4 years of age.[223a] The initial immune response to diphtheria and pertussis vaccines was not determined. Munoz and coworkers[222] also reported that after administration of Hib vaccine at 2 and 4 months' postnatal age, the geometric mean concentration of serum Hib antibody was significantly lower among infants with a gestational age less than 28 weeks than in other infants.

Lau and colleagues[221] reported that the seroconversion rate to hepatitis B vaccine was lower in preterm infants weighing less than 2000 g who were vaccinated soon after birth than in preterm infants vaccinated at a later age or term infants vaccinated shortly after birth. Other investigators have observed a diminished immune response to hepatitis B vaccine among premature infants of lower gestational ages (e.g., less than 33 weeks) or of lower birth weights (e.g., less than 2000 g).[217, 224-226] As a result, administration of the first dose of hepatitis B vaccine for preterm infants born to HBsAg-negative mothers is recommended just before hospital discharge, if the infant already weighs 2000 g, or at age 2 months when other childhood vaccines are recommended.[7, 227, 228]

Several studies suggest that the incidence of adverse events after vaccination of preterm infants is the same as or lower than that of full-term infants vaccinated at the same chronological age.[207, 208, 212, 213] A temporal association between receipt of DTP and Hib vaccine and a transient increase or recurrence of apnea in premature infants has been reported, although the significance of this finding is unclear.[229]

Infants who are born prematurely should be immunized at the same postnatal chronological age and according to the same recommended schedule as full-term infants are.[7, 227] The one exception, as previously discussed, is hepatitis B vaccine. The recommended standard dose of each vaccine should be administered;

divided or reduced doses are not indicated.[7, 227, 230-232] A preterm infant who is still hospitalized at age 2 months can receive the vaccines routinely scheduled at that age. However, because poliovirus vaccine strains are excreted after receipt of OPV, IPV instead of OPV should be administered to hospitalized infants to prevent the risk of poliovirus transmission in the hospital.[7, 227]

BREAST-FEEDING AND IMMUNIZATION

Neither killed nor live vaccines given to a mother or infant who is breast-feeding have adverse consequences.[2, 7] Because killed and inactivated vaccines do not multiply within the body, they pose no special risk for lactating mothers or their infants. Lactating mothers may also safely receive live vaccines, such as yellow fever, MMR, OPV, varicella, and rubella, without interruption of their breast-feeding schedule.[7, 90, 144, 227] Although live vaccines contain attenuated live viruses or bacteria that replicate within the vaccine recipient, most live vaccine strains are not known to be secreted in breast milk. An exception is attenuated rubella vaccine virus, which has been detected in breast milk and recovered from the nasopharynx and throat of some breast-fed infants after maternal immunization.[233-235] In one study, transient seroconversion to rubella virus without evidence of clinical disease was noted in 25% of the breast-fed infants.[233]

Breast-feeding of infants does not adversely affect their development of a protective immune response and is not a contraindication for any vaccine.[7, 144, 236-241] The antibody response to the components of DTP or Hib conjugate vaccines is not inhibited by breast-feeding.[79, 242-244] Vaccination of breast-fed infants results in protective immunity, although doses of OPV administered to these infants during the first 3 days of life may be somewhat less effective than doses administered to older breast-fed infants and infants who are not breast-fed.[79, 237, 238, 240, 245-254] Breast-fed infants who acquired rubella vaccine virus and rubella-specific antibodies from breast milk have a normal immune response to rubella vaccine administered at 15 to 18 months of age.[239]

Compared with infants who are formula fed, breast-fed infants may have an enhanced immune response to certain oral and parenteral vaccines such as conjugate Hib vaccine, OPV, and diphtheria and tetanus toxoids.[244, 255, 256] However, the significance of such an effect is unclear.

Oral rotavirus vaccine is a possible exception to the lack of inhibition by breast-feeding of the immune response to vaccines. Meta-analyses of studies using a single dose of rotavirus vaccines concluded that the immune response to these vaccines was reduced in breast-fed infants.[257, 258] However, the potential inhibitory effect is largely overcome by administration of three doses of vaccine, and no significant decrease in the protective efficacy of rotavirus vaccine is observed in breast-fed compared with non–breast-fed infants.[259, 260]

IMMUNIZATION AND PREGNANCY

Women usually should not receive vaccines during pregnancy unless specifically indicated. This recommen-

dation is based on theoretical concern that a previously unrecognized teratogenic potential from the product administered may occur or that a birth defect unrelated to vaccine will be falsely attributed to the immunization. However, the benefits of vaccination to a pregnant woman in some circumstances outweigh any potential risks, such as if the risk of infection is high, if the infection can have serious consequences for the woman or her fetus, and if the vaccine is unlikely to be associated with an increased incidence of adverse events.[7, 236] Table 5–8 lists vaccines that are indicated and contraindicated during pregnancy.

Use of Live Vaccines

Live vaccines contain attenuated viruses or bacteria that multiply within the vaccine recipient. Because some of the diseases they prevent, such as rubella or varicella, are known to have teratogenic or other serious effects on the fetus, live virus vaccines are usually contraindicated during pregnancy.[7, 227, 236]

Based on a case of vaccine-like rubella virus transmission to a fetus conceived 7 weeks after rubella vaccination, women should be counseled to avoid becoming pregnant for 3 months after receipt of a rubella-containing vaccine.[90, 141, 260a, 260b] Pregnancy should be avoided for 1 month after the receipt of other non–rubella-containing parenteral live virus vaccines, by which time antibody production usually has occurred and vaccine-virus viremia is expected to have ceased.[90, 140, 142, 144] Other practices in dealing with women of childbearing age include asking if a woman is pregnant, not administering live virus vaccine if a woman states that she is pregnant, and explaining the potential risk for the fetus to the woman who states that she is not pregnant.[7, 90] Both OPV and yellow fever vaccine can be administered to pregnant women who are nonimmune and at substantial risk of imminent exposure to infection, such as from impending international travel.[5, 7, 42, 227]

Table 5–8. VACCINATION DURING PREGNANCY

VACCINE	TYPE	INDICATIONS FOR VACCINATION DURING PREGNANCY
Live Virus		
Measles-mumps-rubella	Live attenuated virus	Contraindicated
Poliomyelitis	Trivalent live attenuated virus (oral poliovirus vaccine)	Persons at substantial risk of exposure to polio
Varicella	Live attenuated virus	Contraindicated
Yellow fever	Live attenuated virus	Contraindicated, except if exposure to yellow fever virus is unavoidable
Live Bacterial		
Typhoid	Live attenuated bacteria (Ty21a)	Should reflect actual risks of disease and probable benefits of vaccine
Inactivated Virus		
Hepatitis A	Killed virus	Data on safety in pregnancy are not available; should weigh the theoretical risk of vaccination against the risk of disease
Hepatitis B	Recombinant produced, purified hepatitis B surface antigen	Pregnancy is not a contraindication
Influenza	Inactivated type A and type B virus vaccines	Recommended both for women who will be in the second or third trimester during influenza season and for patients with serious underlying disease; consult health authorities for current recommendations
Japanese encephalitis	Killed virus	Should reflect actual risks of disease and probable benefits of vaccine
Poliomyelitis	Killed virus (inactivated poliovirus vaccine)	Persons at substantial risk of exposure to polio
Rabies	Killed virus	Substantial risk of exposure
Inactivated Bacterial		
Cholera	Killed bacterial	Should reflect actual risks of disease and probable benefits of vaccine
Haemophilus influenzae type b conjugate	Polysaccharide-protein	Only for high-risk persons
Meningococcal	Polysaccharide	Only in unusual outbreak situations
Plague	Killed bacterial	Selective vaccination of exposed persons
Pneumococcal	Polysaccharide	Only for high-risk persons
Typhoid	Killed bacterial or polysaccharide	Should reflect actual risks of disease and probable benefits of exposure
Toxoids		
Tetanus-diphtheria	Combined tetanus-diphtheria toxoids, adult formulation (Td)	Lack of primary series, or no booster within last 10 yr (5 yr, if other than clean minor wounds)
Other		
Immune globulins, pooled or hyperimmune	Immune globulin or specific globulin preparations	Exposure or anticipated exposure to measles, hepatitis A, hepatitis B, rabies, tetanus

Despite precautions, some pregnant women may be inadvertently vaccinated with a live virus vaccine. Available data on these vaccines when they are administered to pregnant women have not demonstrated any serious risk to the mother or fetus.[261-269] Because of the existing safety data and because the risk to the fetus is largely theoretical, administration of a live vaccine during pregnancy is not a reason to consider interrupting the pregnancy.[90, 144] A Varicella Vaccination in Pregnancy Registry, like that which documented the apparent safety of inadvertent rubella vaccination during pregnancy, has been established to monitor prospectively maternal-fetal outcomes in pregnant women inadvertently vaccinated with varicella vaccine (telephone: 800-986-8999).[144, 227]

Use of Inactivated Vaccines

Killed and inactivated vaccines pose no special risk during pregnancy because they do not multiply within the body. Although one study reported an association between administration of IPV during pregnancy and malignant neoplasms of neural origin in offspring,[270] this finding has not been confirmed by other investigators, and IPV can be administered to a pregnant woman who requires immediate protection against poliomyelitis.[7, 42, 227] Other killed and inactivated vaccines and toxoids are not known to be deleterious when they are administered during pregnancy and are sometimes indicated to prevent infection with possible serious outcomes for both mother and fetus. For example, influenza vaccine has recently been recommended for women who will be in the second or third trimester of pregnancy during influenza season because influenza infection may cause increased morbidity in these women.[171, 271]

In some cases, vaccination during pregnancy is intended to protect the fetus or newborn infant from infection. For example, neonatal tetanus remains common in many developing countries where women are not adequately immunized before pregnancy and childbirth and protection of the newborn infant from neonatal tetanus is conferred by placental transfer of maternal antibody from the immune mother.[272, 273] Widespread vaccination of pregnant women in such areas has demonstrated the safety and efficacy of administering tetanus toxoid during pregnancy to prevent neonatal tetanus.[274] In the United States, administration of combined tetanus-diphtheria toxoid is recommended for pregnant women who have not completed a primary vaccination series or who need a booster dose.[7, 158, 236]

Some physicians prefer to wait until the second or third trimester of pregnancy to administer inactivated (killed) vaccines or toxoids.[236] However, no increased risk to the mother or fetus from vaccination during the first trimester has been proved, and vaccination in some cases may be indicated before the second or third trimester. Examples include influenza, hepatitis B, and tetanus-diphtheria vaccines.[7, 58, 171, 227, 236]

Vaccination of Household Contacts

Administration of both live and killed vaccines to household members does not present a known hazard

to pregnant women who are not severely immunocompromised. Although transmission of varicella vaccine virus from a 12-month-old infant to his pregnant mother has been reported, no virus was detected in fetal tissue after an elective abortion.[275] Pregnancy of a mother is not a contraindication to administration of varicella vaccine to her child.[143, 144, 276] However, if a woman is known to be nonimmune to varicella-zoster virus, some physicians may prefer to defer administration of varicella vaccine to her children at least until her third trimester.[143] OPV is the only vaccine contraindicated for household contacts of severely immunocompromised pregnant women.[42, 227]

VACCINATION OF PEOPLE WITH A PERSONAL OR FAMILY HISTORY OF SEIZURES

Infants and young children with either a personal history of convulsions or a parent or sibling with a history of convulsions are at increased risk for a convulsion after receipt of whole-cell pertussis vaccine or MMR (or monovalent measles) vaccine.[277-279] In most cases, these convulsions are brief, self-limited, and associated with fever. Studies have not established a causal association between these convulsions and residual seizure disorders or permanent neurological sequelae.[280, 281] Because acellular pertussis vaccines are less frequently associated with fever than are whole-cell pertussis vaccines, DTaP vaccine is preferred for immunizing children in the United States against pertussis.[81, 150]

Because neurological disorders such as epilepsy or degenerative disorders marked by loss of developmental milestones often become manifest during infancy, DTP vaccination may coincide with onset or recognition of such disorders and cause confusion about the etiological role of pertussis vaccine. For infants with a personal history of a seizure, delaying pertussis vaccination is recommended until a progressive neurological disorder is excluded or the cause of the seizure has been established.[150, 227] Acetaminophen or ibuprofen can be administered at the time of pertussis vaccination and every 4 hours for 24 hours thereafter to reduce the possibility of postvaccination fever.[150] Because measles vaccine is administered at an age when a child's neurological status is likely to have been already established, deferring measles immunization of a child with a personal history of a seizure is not recommended.[90, 227]

Pertussis and measles vaccinations are not contraindicated in persons with a family history of convulsions. Even though children with a parent or sibling who has had a seizure are themselves at increased risk for a seizure, the benefits of administering pertussis and measles vaccine to children with a family history of convulsions substantially outweigh the small risks, because of the benign nature of these seizures.[90, 150, 227, 280, 281]

VACCINATION DURING ACUTE ILLNESS

The decision to administer or delay vaccination because of an intercurrent or recent illness depends on

evaluation of the etiology of the disease and the severity of symptoms.[2, 7] Mild illness, either febrile (≥38°C) or afebrile, is not a contraindication to vaccination with live virus vaccines or inactivated (killed) vaccines.[2, 7] Although one study reported a lower rate of seroconversion to the measles but not to the rubella or mumps components of MMR vaccine in children with evidence of a recent or current upper respiratory infection compared with children without this history, a difference in seroconversion to measles vaccine in healthy children compared with those who are ill has not been found in other studies.[95, 97–100, 117, 282]

Acute minor illnesses, such as upper respiratory infection, diarrhea, and acute otitis media, are common during infancy and childhood.[283] Postponing vaccination in children with minor febrile or afebrile illness constitutes a missed opportunity to protect a child from disease, can contribute to outbreaks of vaccine-preventable disease, and can significantly impede efforts to immunize infants and young children on schedule.[284–288] Every opportunity should be used to provide indicated vaccines and to avoid missed vaccination opportunities in persons who may not return for medical care and administration of recommended vaccines.[2, 7, 289] The potential benefit of preventing disease by timely vaccination far outweighs any small possible risk of vaccine failure.[2]

Vaccination is usually deferred in persons who have moderate or severe illness. A person with signs or symptoms of moderate or severe illness at the scheduled time of vaccination should be requested to return as soon as the illness resolves so that vaccines can be administered at the recommended ages. Waiting until after a person has recovered from the acute phase of a moderate or severe illness avoids superimposing a reaction to vaccination on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine.[2, 7]

ROUTINE CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

Vaccine contraindications and precautions are described in the manufacturer's product labeling and in the recommendations on the use of vaccines developed by national advisory committees such as the ACIP and the Committee on Infectious Diseases of the AAP. In the United States, the content of the product label is regulated by the Food and Drug Administration on the basis of specific studies required of the manufacturer to prove the safety and efficacy of a specific product. Most recommendations of vaccine advisory committees are the same as those in the product label. However, differences sometimes exist because of advisory committees' assessments of the risks and benefits of a given recommendation, their goal to make immunization as practical as possible, and their responsibility to develop recommendations for the use of vaccines in circumstances in which specific safety and efficacy data may be limited but for which physicians, nurses, and public health officials need guidance. For example, the manufacturer's product label recommends that women vaccinated with live virus varicella vaccine avoid becoming pregnant for

3 months, whereas the ACIP and AAP advise waiting only 1 month.[1, 143, 144] Similarly, the AAP and ACIP advise that pregnancy should not be considered a contraindication to hepatitis B vaccination, whereas the manufacturer's product label states that hepatitis B vaccine should be administered to pregnant women only if it is clearly needed.[1, 290]

A contraindication indicates that a vaccine should not be administered. In contrast, a precaution specifies a situation in which vaccine may be indicated if, after careful assessment, the benefit of vaccination to the individual patient is judged to outweigh the risk.[7] Contraindications and precautions may be generic and apply to all vaccines, or they may be specific to one or more vaccines (Table 5–9). The following two guidelines apply to all vaccines: (1) an anaphylactic reaction to a vaccine or vaccine constituent contraindicates further use of that vaccine or vaccines containing that constituent (see *Hypersensitivity to Vaccine Components*), and (2) vaccination is generally contraindicated during moderate or severe acute illnesses regardless of the absence or presence of fever (see *Vaccination During Acute Illness*).

Immunosuppression resulting from underlying disease or therapy is a contraindication for receipt of most live vaccines.[90, 227] An exception is measles vaccine, which is recommended for HIV-infected persons who are not severely immunosuppressed.[90, 227, 291] Corticosteroid therapy can suppress the immune system of an otherwise healthy person, although the minimal dose and duration of therapy necessary to cause immunosuppression are not well defined. Underlying disease, concurrent therapies, and the frequency and route of administration of corticosteroids can also affect immunosuppression. Steroid therapy does not usually contraindicate administration of live virus vaccines when it consists of low to moderate doses administered daily or on alternate days; physiological maintenance doses; or doses administered topically, by aerosol, or by local (e.g., intra-articular) injection.[7, 90, 227] In most cases, persons receiving high doses of systemic corticosteroids (i.e., at least 2 mg per kg per day or 20 mg per day of prednisone or its equivalent) for less than 14 days can receive live virus vaccines immediately after discontinuation of therapy.[2, 7] However, live virus vaccines are not usually administered to persons who have received high doses of systemic corticosteroids for 14 days or more until at least 1 month after cessation of steroid therapy.[90, 227]

Most live virus vaccines are usually contraindicated for pregnant women because of a theoretical risk to the fetus (see *Immunization and Pregnancy*). However, the small theoretical risk from administration of a live vaccine to a pregnant woman is sometimes far outweighed by the risk of contracting a disease with serious consequences for mother and fetus.

Healthcare providers sometimes inappropriately consider a condition to be a contraindication or precaution to vaccination.[2, 7] Withholding vaccine in such instances results in a missed opportunity to administer needed vaccine. A concise summary of appropriate and inappropriate contraindications is given in Table 5–9, adapted from the national *Standards for Pediatric Immunization Practices* (see Chapter 42).

Table 5-9. GUIDE TO CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATIONS*

TRUE CONTRAINDICATIONS AND PRECAUTIONS	NOT CONTRAINDICATIONS (VACCINES MAY BE ADMINISTERED)

General for All Vaccines (DTaP/DTP, OPV, IPV, MMR, Varicella, Hib, Hepatitis B)

Contraindications

Anaphylactic reaction to a vaccine contraindicates further doses of that vaccine

Anaphylactic reaction to a vaccine constituent contraindicates the use of vaccines containing that substance

Moderate or severe illnesses with or without a fever

Not Contraindications

Mild to moderate local reaction (soreness, redness, swelling) after a dose of an injectable antigen

Low-grade or moderate fever after a prior vaccine dose

Mild acute illness with or without low-grade fever

Current antimicrobial therapy

Convalescent phase of illnesses

Prematurity (same dosage and indications as for normal, full-term infants)

Recent exposure to an infectious disease

History of penicillin or other nonspecific allergies or fact that relatives have such allergies

Pregnancy of mother or household contact

Unvaccinated household contact

DTaP/DTP

Contraindications

Encephalopathy within 7 d of administration of previous dose of DTaP/DTP

Precautions[1]

Fever of ≥40.5°C (105°F) within 48 hr after vaccination with a prior dose of DTaP/DTP and not attributable to another identifiable cause

Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hr of receiving a prior dose of DTaP/DTP

Convulsions within 3 d of receiving a prior dose of DTaP/DTP (see footnote 2 regarding management of children with a personal history of seizures at any time)

Persistent, inconsolable crying lasting ≥3 hr, within 48 hr of receiving a prior dose of DTaP/DTP

Guillain-Barré syndrome within 6 wk after a dose[3]

Not Contraindications

Fever of <40.5°C (105°F) after a previous dose of DTaP/DTP

Family history of convulsions[2]

Family history of sudden infant death syndrome

Family history of an adverse event after DTaP/DTP administration

OPV

Contraindications

Infection with HIV or a household contact with HIV infection

Known immunodeficiency (hematological and solid tumors; congenital immunodeficiency; long-term immunosupprssive therapy)

Immunodeficient household contact

Precaution[1]

Pregnancy

Not Contraindications

Breast-feeding

Current antimicrobial therapy

Mild diarrhea

IPV

Contraindication

Anaphylactic reaction to neomycin, streptomycin, or polymyxin B

Precaution[1]

Pregnancy

MMR

Contraindications

Anaphylactic reaction to neomycin or gelatin

Pregnancy

Known immunodeficiency (hematological and solid tumors; congenital immunodeficiency; long-term immunosuppressive therapy; HIV infection with evidence of severe immunosuppression)

Precautions[1]

Recent (within 3–11 mo, depending on product and dose) administration of a blood product or immune globulin preparation

Thrombocytopenia[5]

History of thrombocytopenic purpura[5]

Not Contraindications

Tuberculosis or positive purified protein derivative test response

Simultaneous tuberculin skin testing[4]

Breast-feeding

Pregnancy of mother or household contact of vaccine recipient

Immunodeficient family member or household contact

HIV infection without evidence of severe immunosuppression

Allergic reaction to eggs[6]

Nonanaphylactic reactions to neomycin

Hib

Contraindications

None

Precautions

None

Table 5-9. GUIDE TO CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATIONS* *(Continued)*

TRUE CONTRAINDICATIONS AND PRECAUTIONS	NOT CONTRAINDICATIONS (VACCINES MAY BE ADMINISTERED)

Hepatitis B

Contraindication
Anaphylactic reaction to common baker's yeast

Not Contraindication
Pregnancy

Varicella

Contraindications
Anaphylactic reaction to neomycin or gelatin
Pregnancy
Infection with HIV
Known immunodeficiency (hematological and solid tumors; congenital immunodeficiency; long-term immunosuppressive therapy)

Precautions[1]
Recent (within 5 mo) administration of an immune globulin preparation[7]
Family history of immunodeficiency[8]

Not Contraindications
Immunodeficiency in a household contact
HIV infection in a household contact
Pregnancy in the mother or other household contact of the recipient

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*This information is based on the recommendations of the Advisory Committee on Immunization Practices (ACIP) and of the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP). Sometimes these recommendations vary from those in the manufacturer's product label. For more detailed information, healthcare providers should consult the published recommendations of the ACIP, AAP, the American Academy of Family Physicians, and the manufacturer's product label. These guidelines have been adapted and updated from those published by the U.S. Public Health Service in January 1996.

[1]The events or conditions listed as precautions, although not contraindications, should be carefully reviewed. The benefits and risks of administering a specific vaccine to an individual under the circumstances should be considered. If the risks are believed to outweigh the benefits, the vaccine should be withheld; if the benefits are believed to outweigh the risks (e.g., during an outbreak or foreign travel), the vaccine should be administered. Whether and when to administer DTaP/DTP to children with proven or suspected underlying neurological disorders should be decided on an individual basis. Avoiding administration of certain vaccines to pregnant women is prudent on theoretical grounds. If immediate protection against poliomyelitis is needed, either OPV or IPV is recommended.

[2]Acetaminophen administered before DTaP or DTP vaccination and thereafter every 4 hours for 24 hours should be considered for children with a personal history or a family history of convulsions in siblings or parents.

[3]The decision to give additional doses of DTaP or DTP should be based on consideration of the benefit of further vaccination versus the risk of recurrence of Guillain-Barré syndrome. For example, completion of the primary vaccination series in children is justified.

[4]Measles vaccination may temporarily suppress tuberculin reactivity. MMR vaccine may be administered after, or on the same day as, tuberculin testing. If MMR has been given recently, postpone the tuberculin test until 4 to 6 weeks after administration of MMR. If administering MMR simultaneously with tuberculin skin test, use the Mantoux test and not multiple puncture tests, because the latter require confirmation if positive, which would have to be postponed 4 to 6 weeks.

[5]The decision to vaccinate should be based on consideration of the benefits of immunity to measles, mumps, and rubella versus the risk of recurrence or exacerbation of thrombocytopenia after vaccination, or from natural infections of measles or rubella. In most instances, the benefits of vaccination will be much greater than the potential risks and justify giving MMR, particularly in view of the even greater risk of thrombocytopenia after measles or rubella disease. However, if a prior episode of thrombocytopenia occurred in close temporal proximity to vaccination, it might be prudent to avoid a subsequent dose.

[6]Recent data suggest that most anaphylactic reactions to measles- and mumps-containing vaccines are associated with hypersensitivity not to egg antigens but to other components of the vaccines. Because the risk of anaphylactic reactions after administration of measles- or mumps-containing vaccines in persons who are allergic to eggs is extremely low and skin testing with vaccine is not predictive of allergic reactions to these vaccines, skin testing and desensitization are no longer required before administration of MMR vaccine to persons who are allergic to eggs.

[7]Varicella vaccine should not be administered for at least 5 months after administration of blood (except washed red blood cells) or plasma transfusions, immune globulin, or varicella-zoster immune globulin (VZIG). Immune globulin or VZIG should not be given for 3 weeks after vaccination unless the benefits exceed those of the vaccination. In such cases, the vaccinee should either be revaccinated 5 months later or tested for immunity 6 months later and revaccinated if seronegative.

[8]Varicella vaccine should not be administered to a member of a household with a family history of immunodeficiency until the immune status of the recipient and other children in the family is documented.

DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; DTP, diphtheria and tetanus toxoids and whole-cell pertussis vaccine; Hib, *Haemophilus influenzae* type b vaccine; HIV, human immunodeficiency virus; IPV, inactivated poliovirus vaccine; MMR, measles-mumps-rubella virus vaccine; OPV, oral poliovirus vaccine.

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